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Cross Species Extrapolation and Hazard Identification in Neurotoxicology

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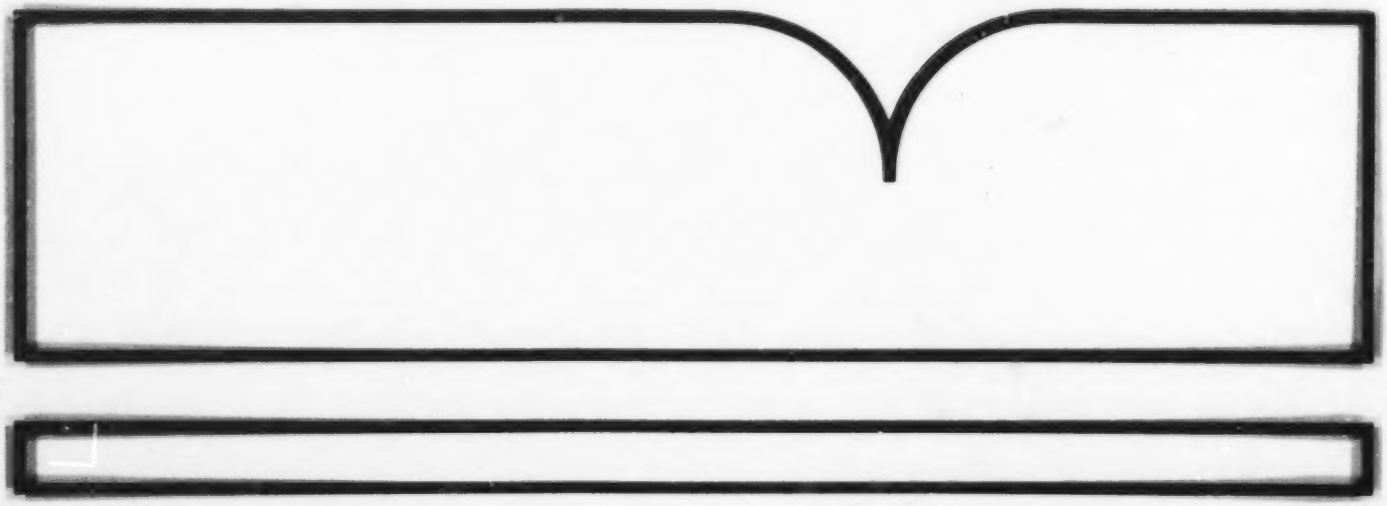

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16. ABSTRACT

Two issues essential to the cross-species extrapolations process are considered: the endpoints to which extrapolation is intended (target end points) and the end points from which extrapolation is intended (source end points). Different types of target and source end points are identified and discussed.

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COMMENTARY

Cross Species Extrapolation and Hazard Identification in Neurotoxicology[1]

ROBERT S. DYER

Neurophysiology Branch, Neurotoxicology Division, U.S. Environmental Protection Agency Research Triangle Park, NC 27711

THE first step in risk assessment is hazard identification. To predict hazard, rather than assess damage in human populations *post hoc*, it is necessary to extrapolate from animal data to human health. In contemplating the cross-species extrapolation process, and in designing animal experiments as the basis for such extrapolation, there are a number of different issues which should be recognized. The purpose of this commentary is to consider two of these issues: the endpoints to which we wish to extrapolate (the "human" or target endpoints), and the endpoints from which we wish to extrapolate (the "animal" or source endpoints). Other issues, such as predicting an effective dose in one species based upon dose/effect data in another, are predicated on an understanding of the source and target endpoints and the relationship between them.

TARGET ENDPOINTS

There is a fundamental difference in the cross-species extrapolation process of neurotoxicologists and that of clinical neurologists. A neurologist usually wishes to extrapolate from animal data to a known human disease entity using known markers of dysfunction. Indeed, existence of the disease entity provides the motivation for developing animal models from which to extrapolate. The identification of a successful model in this case enables exploration of the mechanism of disease, which in turn may lead to effective prevention, treatment or cure. In contrast, the neurotoxicologist often wishes to model normal human function, so that significant and potentially novel alterations in such function can be detected. There are of course exceptions. For example, when there is a previously described neurotoxic disease state in humans (e.g., OPIDN), then the problem reverts to that of the clinical neurologist. Presumably we have not yet discovered all possible types of neurotoxic disease state in humans, and in fact we would like to prevent as many as possible from ever being clearly demonstrated in humans. We are faced therefore with modelling normal function and detecting deviations from it, rather than modelling disordered function.

In many ways, modelling normal function is by far the more difficult process. After all, which function is it that one wishes to model? This is the crux of the target endpoint problem. With respect to detection of health effects, there are four fundamental types of target endpoints, differing in the extent to which alterations in them may be regarded as indicative of an adverse health effect. In practice, the four types of endpoints exist on a continuum. Implicit in the distinction between types of target endpoints is the assumption that one knows what constitutes a health effect.

Type I target endpoints are those which virtually define a health effect. For example, death is a type I endpoint, the presence of which is sufficient to indicate without further discussion that an adverse health effect has occurred. In carcinogenesis, increased tumor incidence is a type I endpoint. In neurotoxicology there are few type I endpoints, although grand mal seizures, paralysis, and blindness would all be included in this category.

Type II target endpoints are those from which an adverse health effect is inferred based upon a strong correlation with previous observations. Most toxicologists would agree that these endpoints reflect dysfunction, but the strength of the inference and the significance of such findings depend upon qualitative and quantitative variables. One example of a type II endpoint which might be confused with a type I endpoint is a brain lesion. If the maximum size of a brain lesion produced by exposure to very high dosage of a compound was very small (e.g., loss of 100 cells) and if it occurred in a relatively large area of the brain (e.g., frontal cortex), then it is easy to imagine disagreement regarding whether this represented a health effect. Slowed nerve conduction velocity also falls into this category. While few would disagree that gross slowing of peripheral nerve conduction velocity is indicative of dysfunction, conduction velocity is not the target health effect. Physicians do not receive complaints of slowed conduction velocity. Rather, the slowed conduction velocity is an indicator that there may be sensory or motor dysfunction, the magnitude and seriousness of which depend upon the magnitude of slowing. A further example of the type II target endpoint is decreased IQ test score. Again, a reduced IQ test score is not in itself an adverse health effect. However to the extent that IQ test results correlate with "intelligence" and the ability to function in society, they are assumed to reflect human health.

[1]This manuscript has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency and approved for publication. Opinions represent those of the author, not the Agency. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

TABLE 1

CROSS-SPECIES EXTRAPOLATION ENDPOINTS

Source (Animal) Endpoints	Target (Human) Endpoints
TYPE A—Identical to some target endpoint	TYPE I—Virtually define health effect
TYPE B—Apparently the same as (homologous with) some target endpoint	TYPE II—Known to be highly correlated with health effect
TYPE C—Models of target endpoints	TYPE III—Presumption of relationship with human health based on some data
TYPE D—No known relationship to a target endpoint	TYPE IV—Little information available relating to human health

Type III endpoints are those for which there is some presumptive evidence of a relationship to human health. It is important to note that the indirect relationship between type III target endpoints and health effects is not necessarily a function of measurability, but rather a reflection of ignorance regarding the significance for the whole organism of changes in the endpoint. Examples of this type of endpoint are EEGs, evoked potentials, locomotor activity, nervous system-specific phosphoproteins, etc. In many respects this category of target endpoints is the most important, because it includes a large quantity of accessible target endpoints with corresponding (type A or type B, see below) source endpoints. Type III endpoints should be considered transitional, in that further research will either elevate them to type II status, or relegate them to type IV status. Clinical neurotoxicologists should consider the accurate disposition of type III target endpoints to be a primary responsibility.

Finally, the type IV target endpoint is one for which there is either no known or at best a minimal relationship between human health and changes in the variables measured. The absence of a large number of candidates for this category is less a cause for self congratulation than it is a statement of the inattention given to the disposition of type III endpoints. Presumably the type IV category will expand as we carefully scrutinize type III target endpoints.

Careful attention must be given to our target endpoints. Little benefit can be gained from an extrapolation-motivated research program which painstakenly delineates the steps required to extrapolate to type IV target endpoints.

SOURCE ENDPOINTS

The effort devoted to the extrapolation enterprise should depend not only on the worthiness of the target human endpoint, but also on the type of endpoint FROM which extrapolation is to be attempted.

A convenient way to define and describe source endpoints is in terms of the nature and strength of their relationship to the human target endpoints. While these relationships exist along a continuum of directness it is convenient to think of them as falling into one of four types. Type A, the most desirable yet elusive, is one which is unequivocally identical in humans and non-humans. The most obvious example of this is death. Another example might be a particular type of tumor (e.g., mesothelioma), or existence of a specific peripheral nerve lesion. Since type A source endpoints carry the presumption of identical mechanism, it may be difficult, even in the case of death, to categorize them unequivocally.

Type B source endpoints only appear to be the same as their human counterparts. In a sense they are homologues. These are potentially dangerous endpoints because they may lead in the hands of the incautious to fallacious inferences. Many endpoints must be placed into this category pending further experimentation to determine their fitness for the "identical" (type A) label. Temporary residence of one's pet endpoint in this category is not cause for undue alarm, but is rather a signal that attention must be directed to determining the relationship between this endpoint and its apparently identical human counterpart. Examples in the neurotoxicology field are locomotor activity, EEGs, and evoked potentials. While it is possible to measure these endpoints in human and non-human species, it is by no means certain that the neural mechanisms underlying the endpoints are identical, or that alterations in the endpoints would have the same interpretation in all cases.

The type C source endpoints are clearly models for human endpoints. Investigators make no pretense that the method is identical to the human endpoint, but rather claim that the endpoint models in some significant way the target endpoint. Examples of type C endpoints are the Ames test, a model for carcinogenesis, and the metrazol seizure model for neuronal excitability. In the latter case, the assumption is made that latency or severity changes in rats using this method are predictive of diffuse neurological disturbances in humans. Another type C endpoint is acquisition of bar pressing as a model for human learning. It should be pointed out that while there may be human counterparts to these endpoints (i.e., one can teach a human to bar press), it is not usually the intent of studies using these endpoints to extrapolate to human bar-pressing behavior.

Finally, a type D source endpoint is one in which there is only the investigator's hope and belief that a correlation will be established with a human endpoint. To avoid being inflammatory, no examples will be provided. However investigators should either (a) convince themselves that they do not work on such endpoints, or (b) take steps to discover the relationship of the source endpoint to a human counterpart.

EFFORT AND EXTRAPOLATION

The process by which we learn more about our target and source endpoints is known as validation. Do they really measure what we think they measure? It should be apparent that the validation process applies within target and source endpoint groups as well as between them. Fortunately there is an extensive psychological literature dealing with problems of validation, and hopefully this literature can be used by the neurotoxicologist engaged in the process [1].

The different types of source and target endpoints are summarized in Table 1. Clearly any attempt at extrapolation from animal data to human health may involve any of the 4 types of target endpoints and any of the 4 types of source endpoints. However the efficient investigator will consider carefully both classes of endpoints before embarking upon an extrapolation-oriented research effort. It makes no more sense to extrapolate from a type A source endpoint to a type 4 target endpoint, than it does to extrapolate from a type D source endpoint to a type 1 target endpoint.

The purpose of this commentary has been to identify some of the issues involved in the endpoint-extrapolation process. Only by appreciating the nature and limitations of intended extrapolation can we succeed in this vital and difficult enterprise, and only after such a satisfactory endpoint-extrapolation process does it make sense to consider the issue of dose extrapolation.

REFERENCES

1. Cronbach, L. J. *Essentials of Psychological Testing*, 3rd Edition. New York: Harper & Row, 1970.

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